Clinician-targeted interventions to reduce antibiotic prescribing for acute respiratory infections in primary care

An overview of systematic reviews

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Clinician-targeted interventions to reduce antibiotic prescribing for acute respiratory infections in primary care: an overview of systematic reviews (Protocol)

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[Overview of Reviews Protocol]

Clinician-targeted interventions to reduce antibiotic prescribing for acute respiratory infections in primary care: an overview of systematic reviews

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To systematically review the literature and appraise the existing evidence from systematic reviews regarding the effects of interventions, aimed at changing clinician behaviour, to reduce antibiotic prescribing for ARIs in primary care.

BACKGROUND

Description of the condition

Antibiotic resistance is recognised as a major threat to human health worldwide (WHO 2015). Each year in the USA, at least two million people become ill with antibiotic-resistant infections and at least 23,000 people die as a direct result of these infections (CDC 2013). People with infections caused by drug-resistant bacteria are generally at increased risk of worse clinical outcomes and death, and consume more healthcare resources than people infected with the same bacterial species that are not drug-resistant (WHO 2015). Estimates suggest that an additional 10 million deaths may occur by 2050 from drug-resistant bacterial infections. In addition, by the same time point, such infections could cost the global economy around USD 100 trillion, through a reduction in overall economic production as a result of mortality and morbidity in the labour force (RAR 2014). A recent evaluation also identified that previous research, which estimated the cost of antimicrobial resistance at USD 55 billion year in the USA, may have underestimated the cost of antibiotic resistance and that the real cost may be much higher (Smith 2013).

Antibiotic use inevitably causes antibiotic resistance as the use of antibiotics naturally selects for pre-existing antibiotic-resistant populations of bacteria (Spellberg 2013). Globally, human consumption of antibiotics increased by 36% between 2000 and 2010, which was also reflected in European data that indicated increases in antibiotic prescription (Adriaenssens 2011; Van Boeckel 2014). In 2013 in the UK, 949.9 tonnes of antibiotics were used for

both people and animals, with 56% of the total use being for human consumption (PHE 2013). For an individual patient, recent antibiotic use is the single most important risk factor for infection with an antibiotic-resistant bacterial species (Chung 2007; Malhotra-Kumar 2007). In addition, longer and multiple courses of antibiotics are associated with higher rates of resistance (Costello 2010). In the last few decades, drug companies have invested little in the discovery and development of new antimicrobial drugs, which are urgently needed to help tackle emerging drug-resistant bacterial strains (Huttner 2013). Whilst efforts to engage the pharmaceutical industry are needed, it is crucial that strategies to promote more prudent use of antibiotics are also undertaken.

Various approaches are available to achieve more prudent antibiotic prescribing for people. Strategies include promotion of narrow-spectrum over broad-spectrum antibiotics, and prescribing the shortest and clinically effective course. However, the most significant component of more prudent prescribing is the reduction in prescriptions of antibiotics. Most antibiotics are prescribed in primary care, with the most common indications for antibiotics being respiratory infections (ARIs) (Goossens 2005; Gulliford 2014; Shapiro 2014). ARIs include community-acquired pneumonia, which usually requires antibiotics, and there may be other presentations (e.g. acute exacerbation of chronic obstructive pulmonary disease (COPD)) which may also benefit from antibiotics. However, these comprise a minority of ARIs seen in primary care. Whilst antibiotics may be of clinical benefit in a minority of cases, people often present with acute and self-limiting infections for which antibiotics offer little or no benefit and increase risk of harm through adverse events and antibiotic resistance. One-third fewer children with acute otitis media had pain at day 2 to 3 (number needed to treat for an additional beneficial outcome (NNTB) = 20) (Venekamp 2015), and the duration of sore throat and acute bronchitis (cough) was reduced by 12 to 16 hours (NNT to prevent one sore throat = 21) with antibiotics (Smith 2014; Spinks 2013). Meanwhile, the risk of vomiting, diarrhoea or rash increased (number needed to harm (NNTH) = 9 for acute otitis media, and NNTH = 24 for acute bronchitis). As such, the management of ARIs is a prime area where overprescription of antibiotics is common and offers potential for clinician-targeted interventions to change antibiotic-prescribing behaviour.

Description of the interventions

The prescription of an antibiotic is a distinct behaviour which is performed by a clinician and in which the clinician has ultimate control. Many interventions designed to target clinicians also frequently target patients or the public, or both, and in doing so, provide a holistic approach that acknowledges the various stakeholders involved in antibiotic prescribing and supports each group in carrying out particular desirable behaviours. However, an antibiotic cannot ultimately be prescribed without the prescribing clinician's consent. In this respect, although several factors may influence the decision to prescribe an antibiotic, such as the patient presentation and wishes of the patient, the actual outcome of whether a prescription is written or not depends on the clinician's decision. As such it is crucial to understand how interventions target this specific population. Consequently, in this overview we will focus on interventions aimed at clinicians to reduce antibiotic prescribing for people with ARIs in primary care. We included all ARIs in this definition although we would not expect to identify interventions to reduce antibiotic prescribing in conditions where antibiotics may be beneficial, such as pneumonia. We included the following interventions:

1. educational materials for clinicians: printed, electronic or audio-visual materials that target the healthcare professional;
2. educational meetings: healthcare professionals attending conferences, lectures, training courses or workshops;
3. educational outreach visits: healthcare professionals receiving information from a trained professional in their practice setting;
4. audit and feedback: any summary of clinical performance of health care over a specified time period provided to the healthcare professional;
5. reminders: verbal, written or electronic information intended to prompt a healthcare professional to recall information;
6. financial interventions: targeting the healthcare professional to include financial incentives (e.g. fee-for-service) and financial penalties (e.g. direct or indirect financial penalty for inappropriate behaviour);
7. point-of-care tests: equipment for use by healthcare professionals in their practice setting to provide diagnostic information to help reduce the uncertainty associated with clinical diagnosis;
8. communication strategies: any resource targeted at the healthcare professional which encourages discussion with a patient about management options including:
   i) clinician-delivered patient educational interventions;
   ii) improved communication interventions (for clinician-patient interaction);
   iii) shared decision making (as defined by Coxeter 2015);
9. mass media campaigns: targeted at the healthcare professional at the population level using varied use of communication; and
10. delayed prescription strategy: any resource targeted at the healthcare professional that encourages giving a prescription for a patient to collect or use at a later date than the initial consultation.

How the intervention might work

A large body of literature has examined the effectiveness of various types of interventions, including combinations of interventions. Educational materials for clinicians have been a major focus. How-

ever, these assume a knowledge deficit and do not acknowledge potential barriers to following recommendations in practice. As such, they are likely to have only a limited effect on behaviour and are often not enough to initiate significant change (NICE 2008). On a broader scale, any single intervention is unlikely to have a major effect on behaviour due to the multiple factors that influence an antibiotic-prescribing decision. These factors can relate to the clinical presentation of the illness (e.g. diagnostic uncertainty), the social influences in a primary care consultation (e.g. patient expectations for antibiotics) and the environment in which a prescribing decision is made (e.g. clinician workload) (Tonkin-Crine 2011). In order for an intervention to have the maximum effect on a specific behaviour it must work to address these various mechanisms of behaviour change synergistically. Given this, a multifaceted approach to developing interventions to change behaviour seems to have most potential (Arnold 2005). As a result, previous research has frequently trialled several interventions in combination rather than testing single interventions alone. The evaluation of intervention types is therefore complicated and is constrained by this type of study design.

Why it is important to do this overview

Antibiotic prescribing is a major driver for the development of antibiotic-resistant infections in the community and is common in the management of ARIs in primary care. The volume of research and range of proposed interventions aimed at the reduction of antibiotic prescribing for ARIs is rapidly growing although their effectiveness at changing behaviour is varied. A number of systematic reviews have evaluated the effectiveness of individual interventions but this evidence, on all types of intervention, has not been synthesized. An overview of the research will help identify the range of interventions in this area and the supporting evidence to determine which are most effective at changing antibiotic-prescribing behaviour. This overview will provide a synthesis of the evidence from published systematic reviews on interventions that target healthcare professional antibiotic prescribing for ARIs. The overview will bring together all of the high quality systematic reviews of any clinician-targeted intervention to reduce antibiotic prescribing for any ARI in primary care, and could be a reference document for decision makers and clinicians to review the evidence in this area. The results will inform future guidelines and identify any gaps in the current evidence base.

OBJECTIVES

To systematically review the literature and appraise the existing evidence from systematic reviews regarding the effects of interventions, aimed at changing clinician behaviour, to reduce antibiotic prescribing for ARIs in primary care.

METHODS

Criteria for considering reviews for inclusion

Types of reviews

In this overview of reviews, we will include all published systematic reviews (Cochrane and non-Cochrane) of randomised controlled trials (RCTs) (to include parallel-group, cluster and factorial) testing interventions that aim to decrease antibiotic prescribing in primary care for acute respiratory infections (ARIs). We will include reviews that include primary studies of non-RCT designs but only where RCT data are reported separately. We will include reviews that include studies from a variety of primary and ambulatory care settings (e.g. general practices, out-of-hours centres, emergency departments). We will also include reviews with studies that recruited participants from hospital inpatient settings, as well as primary or ambulatory care settings, providing data from the latter are reported separately.

Types of participants

We will include reviews that studied interventions targeted at the antibiotic-prescribing behaviour of clinicians for the treatment of ARIs in primary care. Healthcare professionals will include any professional qualified to prescribe antibiotics to people. Primary care will include all contexts in which outpatients are managed in the community as the first point of patient contact to include general practice and out-of-hours services, inclusive of emergency departments. We will exclude reviews that purely focused on healthcare professionals working in inpatient settings, including hospitals and residential settings such as nursing homes.

Participant populations studied within reviews will include any participant, of any age, who presented in a primary care context (as above) with an ARI. ARI is defined as any sudden onset respiratory infection.

Types of interventions

We will consider all types of interventions targeted at changing the antibiotic-prescribing behaviour of healthcare professionals for the management of ARIs in primary care. We will include the following interventions: educational materials for clinicians, educational meetings, educational outreach visits, audit and feedback, reminders, financial interventions, point-of-care tests, communication strategies, mass media campaigns and any other relevant intervention not covered by the previous categories. We will include interventions whether they target healthcare professionals as a single population or healthcare professionals as one of several groups of interest.

Types of outcome measures

Primary outcomes

1. Change in antibiotic prescriptions for ARI (total number prescribed or proportion of participants prescribed antibiotics, to include a delayed prescription).

Secondary outcomes

1. Prescribing outcomes:
   i) proportion of participants with an ARI given an antibiotic prescription for immediate use;
   ii) proportion of participants with an ARI given a delayed antibiotic prescription;
2. participant outcomes:
   i) proportion of participants with an ARI colonised or infected with antibiotic-resistant bacteria;
   ii) adverse events;
   iii) symptom duration or severity;
   iv) health-related quality of life;
   v) participant satisfaction;
   vi) any measure of management failure, e.g. re-consultation for the same illness, hospital or emergency department attendance; and
3. healthcare resource costs:
   i) management costs for any medication for the treatment of an ARI or associated complications.

Search methods for identification of reviews

We will search the Cochrane Database of Systematic Reviews (CDSR) to identify all relevant published Cochrane systematic reviews of interventions to change the antibiotic-prescribing behaviour of healthcare professionals in primary care for ARI. In order to identify any other relevant systematic reviews we will search the following five databases: MEDLINE (from 1946), EMBASE (from 1974), CINAHL (from 1982), PsychINFO (from 1967), Web of Science (from 1945). An Information Specialist, in consultation with the review authors and the Cochrane ARI Group Information Specialist, developed the MEDLINE search strategy (Appendix 1). We will not apply any language restrictions.

Data collection and analysis

Selection of reviews

Two review authors (STC and KW/OvH/AMcC/MPH) will independently screen all titles and abstracts received from the literature searches to identify potentially eligible reviews based on the following criteria:

1. review included RCTs or parallel-group, factorial or cluster-RCTs;
2. participants in studies included in the review were people who presented in primary care settings with ARIs;
3. investigated single or multifaceted interventions whose primary aim is to reduce antibiotic prescribing by targeting the behaviour of healthcare professionals; and
4. investigated the effect of the intervention on antibiotic prescribing when compared with usual care or the control intervention.

We will obtain full texts of reviews we identify as potentially eligible for inclusion. Two review authors (STC and KW/OvH/AMcC/MPH) will screen full-text papers. We will agree on inclusion of reviews by consensus, through discussion with a third review author where necessary. We will report the review selection process using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram. Authors will list the excluded reviews (after assessment of full-text articles) and reasons for exclusion in a 'Characteristics of excluded reviews' table.

Data extraction and management

Two review authors (STC and KW/OvH/AMcC/MPH) will independently extract data on the characteristics of included systematic reviews using a standardised data extraction form. The form will cover the following information:

1. general information (title, authors, study ID);
2. aims and rationale;
3. extent of search (databases searched, restrictions);
4. eligibility criteria (including type of studies included and whether RCTs reported separately);
5. participants;
6. interventions (type, target population);
7. comparator(s);
8. outcomes assessed; and
9. conclusions and recommendations of the review.

If necessary, we may seek additional information from the authors of included systematic reviews or occasionally from the authors of primary studies included in systematic reviews. Where data from a given study are included in multiple reviews, we will report the extent of the overlap between reviews and assess the impact of this in interpreting the results of the reviews. This will involve considering how individual studies have been interpreted by the authors of each systematic review, the number of studies included in the review and the likely influence of an individual study on the review findings. If two reviews completely overlap regarding the studies they include, we will only include one of the reviews in the overview. Two review authors (STC and KW/OvH/AMcC/MPH) will discuss which review should contribute data to the overview based on the outcomes and comparisons explored, search end date and 'Risk of bias' assessment (see below). We will present a summary of the included reviews in a 'Characteristics of

included reviews' table (Higgins 2011). This table will include information on the population studied, interventions, comparison intervention, outcomes for which data were reported and a brief description of any limitations of methods used in each review.

Assessment of methodological quality of included reviews

Reviews will have to meet a minimum quality criteria in order to be included in the synthesis. Two review authors (STC and KW/OvH/AMcC/MPH) will independently assess the methodological quality of each systematic review using the ROBIS tool (Whiting 2016). ROBIS is used to assess the risk of bias in systematic reviews using three phases. Phase 1 assesses relevance of included reviews, phase 2 assesses four domains through which bias may be introduced into an overview and phase 3 assesses the overall risk of bias in the interpretation of the overview findings (Whiting 2016). We will assess domains in phase 2 as high or low concern or unclear findings. We will assess phase 3 as either high or low risk of bias. We will resolve any differences in quality assessment by discussion, and if necessary we will consult a third review author. We will exclude systematic reviews for which the ROBIS tool suggests a high risk of bias. We will note differences in quality between included reviews and take these into consideration in the interpretation of the results of reviews and the overall synthesis reported in this overview.

Two review authors (STC and KW/OvH/AMcC/MPH) will examine the included reviews for information on eligibility of included trials, risk of bias and the results of any meta-analysis performed. Where information is provided by the authors of each systematic review, we will extract and report this in the overview. We will make comparisons between reviews about the data reported to assess whether judgements made about quality of evidence are similar between reviews. For any included review where an assessment of quality of evidence is not provided, we will perform a retrospective analysis using the 'Risk of bias' tool and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool (Guyatt 2008; Higgins 2011).

Data synthesis

We will provide a narrative synthesis of all the results of the included systematic reviews. We will present a summary of data using an 'Overview of reviews' table and will give details of reviews based on all relevant outcomes. Data will include details of the intervention and comparison intervention, effect of the intervention relative to the control intervention, the number of participants and studies, quality of the evidence and any other important comments about the review, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If we identify any sources of heterogeneity based on the characteristics of studies in included reviews, we will perform a sensitivity analysis and report a summary table.

Subgroup analyses are dependent on the data available from the included reviews, where data from RCTs are reported. We aim to conduct subgroup analyses in the following areas:

1. adults (aged 18 years and over) versus children;
2. placebo versus no intervention; and
3. combined versus single interventions.

We will perform both subgroup and sensitivity analyses in relation to the primary outcomes and adverse effects only. We will carry out statistical analysis using the Review Manager software (RevMan 2014) where appropriate. We will present results in a 'Summary of findings' table (Higgins 2011).

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The views expressed are those of the protocol authors and not necessarily those of the UK National Health Service, the National Institute of Health Research (NIHR) or the UK Department of Health.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

The researchers created a Medline (Ovid) Search strategy which was combined with the best balance of sensitivity and specificity from the Health Information Research Unit at McMaster University (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Reviews).

1. exp Anti-Bacterial Agents/ OR (Antibacterial? or Anti-bacterial? or Antibiotic? or Anti-biotic? or Macrolide? or beta-Lactam? or Antimicrobial? or Anti-microbial? or Penicillin or Methicillin or ampicillin or azithromycin or Cephalexin).tw.

2. exp Respiratory Tract Infections/ OR ((respiratory OR chest) adj3 (infect* or inflam*)).tw. OR (ARI OR ARTI OR URTI OR LRTI).tw. OR Nasopharyngitis/ OR (nasopharyngit* or rhinopharyngit*).tw. OR exp Sinusitis/ OR sinusit*.tw. OR (nasosinusit* or rhinosinusit*).tw. OR Rhinitis/ OR rhinit*.tw. OR (rhinorrhoea or rhinorrhea).tw. OR ((runny or running or discharg* or congest* or blocked or stuff* or dripping) adj2 (nose* or nasal)).tw. OR exp Pharyngitis/ OR pharyngit*.tw. OR sore throat*.tw. OR (throat* adj3 (inflam* or infect*)).tw. OR tonsillit*.tw. OR Laryngitis/ OR laryngit*.tw. OR croup.tw. OR (pseudocroup or tracheobronchit* or laryngotracheobronchit*).tw. OR Bronchitis/ or exp bronchiolitis/ or bronchiolitis, viral/ OR (bronchit* or bronchiolit*).tw. OR exp Pneumonia/ OR (pneumon* or pleuropneumon* or bronchopneumon*).tw. OR exp Pleurisy/ OR pleurisy.tw. OR Cough/ OR Sneezing/ OR (cough* or sneez*).tw. OR exp Otitis Media/ OR (otitis media or aom or ome).tw. OR Earache/ OR earache*.tw. OR Influenza, Human/ OR (influenza* or flu).tw. OR Common Cold/ OR common cold*.tw.

3. exp Drug Prescriptions/ OR Inappropriate prescribing/ OR Practice Patterns, Physicians/ OR (prescrib* OR prescrip* OR stewardship OR Antibiotic therapy OR Antibiotic treatment).tw.

4. (Delay OR Delayed OR Reduce OR Reduces OR Reducing OR Reduced OR Discontinue OR Stopping).ti,ab.

5. Ambulatory Care/ OR exp Ambulatory Care Facilities/ OR exp general practice/ OR
exp general practitioners/ OR exp physicians, family/ OR exp physicians, primary care/ OR exp Primary Health Care/ OR exp Office Visits/ OR Outpatients/ OR (ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab. OR (practi* or physician? or doctor? OR Clinician?).ti,ab. OR (primary care OR primary health care OR primary healthcare).ti,ab. OR (after hour? or afterhour? or "out of hour?" or ooh).ti,ab. OR (clinic? or visit?).ti,ab. OR ((health* OR medical) adj2 (center? or centre?)).ti,ab. OR outpatient?.ti,ab. OR exp Emergency Service, Hospital/ OR Emergency Medical Services/ OR (emergency adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.

6. meta-analysis.mp,pt. OR review.pt. OR search*.tw.

7. 1 AND 2 AND 3 AND 4 AND 5 AND 6

CONTRIBUTIONS OF AUTHORS

Sarah KG Tonkin-Crine, Kay Wang and Oliver van Hecke wrote the first draft of this protocol. All review authors edited the protocol draft and approved the final version.

DECLARATIONS OF INTEREST

Sarah KG Tonkin-Crine is a Health Psychologist funded by the NIHR Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance at the University of Oxford.

Kay Wang is a NIHR Academic Clinical Lecturer in General Practice at the University of Oxford. The Cochrane Review Support Programme has awarded the review team a conditional grant to support this work.

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Nia Roberts: none known.

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Malene Plejdrup Hansen is a postdoctoral fellow at the CREMARA funded by the NHMRC, Australia (1044904).

Christopher C Butler has held research grants to develop, evaluate and implement antibiotic stewardship interventions. He has received honoraria from Alere and Roche for contributions about point of care diagnostics. He is the chief investigator of the publicly funded PACE study that is assessing C-reactive protein point of care testing (CRP POCT) to guide antibiotic treatment for acute exacerbations of chronic obstructive airways disease: Alere has provided the CRP POCT devices and associated support as an unconditional educational grant free to the study. He also receives support from the NIHR Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance at the University of Oxford, and holds several publicly funded grants to conduct research in the field of infections.

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